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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,000	11/14/2003	Vanessa Chisholm	P1746R1P1	1570

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,000	CHISHOLM ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-115* is/are pending in the application.

4a) Of the above claim(s) *91,92,100,101,112 and 114* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-90,93-99,103,105-111,113,115 and 116* is/are rejected.

7)☒ Claim(s) *102 and 104* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5 submissions*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 59-116 are pending in this application.

Election/Restrictions

Applicant's election without traverse of group I, claims 59-90, 93-99, 102-111, 113 and 115-116 in the reply filed on 06/29/2005 is acknowledged. Therefore, claims 91-92, 100-101, 112 and 114 are withdrawn from further consideration as drawn to nonelected subject matter.

Sequence Compliance

Figures 13A and 13B disclose amino acid sequences that are not properly identified with sequence identifiers (i.e. "SEQ ID NO:"). Sequence Listing, See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431. The requirement for a sequence listing applies to all sequences disclosed in a given application, whether the sequences are claimed or not. See MPEP § 2421.02. If said sequences were originally submitted in both electronic and paper format, then applicant is only required to make proper amendment to the Brief Description of the Drawings (i.e. with proper sequence identifiers). However, if applicant has not previously submitted said sequences then a new submission is also required (i.e., CD-ROM/CD-R, paper copy and Attorney Declaration).

Claim Objections

Claims 106, 108 and 109 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

As written, claims 106 and 109 expand the number of genes comprising the fusion gene to a third gene encoding puromycin resistance fused to a (fourth) gene encoding DHFR. To be further limiting, the claims must be amended to recite "the first selectable gene" and "the amplifiable second selectable gene", which is presumably what is intended.

Similarly, claim 108 expands the number of genes comprising the fusion gene to a third fluorescent protein gene fused to a gene encoding DHFR.

In addition, claim 71 objected to because of the following informalities. The claim would be more precise if the term "positioned" were inserted before the term "between" to remove any potential ambiguity with respect to the limitation directed to the IRES and its relation with the selected sequence and the fusion gene (e.g., as is used in claim 72 regarding various polynucleotide structural elements). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 88, 97, 103 and 115 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claims 88 and 97 recite the limitation "the amplifiable selectable gene" which lacks sufficient antecedent support. The independent claims 59 and 72 respectively corresponding to claims 88 and 97, recite "an amplifiable second selectable gene".

Similarly, claim 115 omits the term "second" in the limitation "the amplifiable selectable gene" thus lacks sufficient antecedent support with respect to base claim 59. It would be remedial to insert the term "second" into the cited limitation.

Claim 103 contains the trademark/trade name HERCEPTIN. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an antibody and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

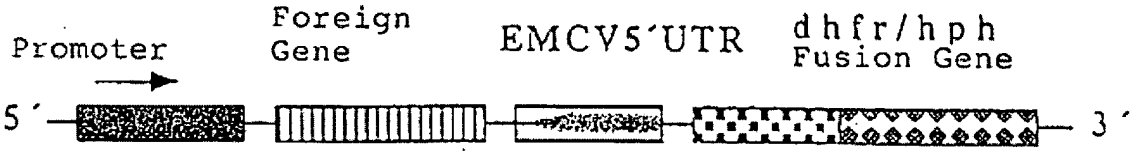
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. **Claim 59-66, 80-81, 84-87, 89-90 and 115 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Herlitschka et al. (US 6,114,146; see entire document; hereinafter the '146 patent).**

The '146 patent teaches expression vectors, tansformed cells and methods of utilizing the same to produce foreign proteins in said transformed cells, wherein the expression vector contains a dicistronic transcription unit. (e.g., Abstract). More particularly, the '146 patent teaches a vector (i.e., polynucleotide) comprising a promoter, a foreign gene (i.e., selected sequence encoding a desired product) and a fusion gene comprising a first selectable gene and an amplifiable gene as is depicted in Figure 1:

FIG. 1



As the figure demonstrates, DHFR is fused with *hph* which is gene encoding an antibiotic selectable protein (i.e., hygromycin B phosphotransferase; claims 59-64, 66 and 115). (col. 14, l. 65). The reference further teaches that an example of a foreign gene is human factor VIII, which meets the broad limitation of a receptor (e.g., Factor VIII binds a host of cellular factors, such as lipoprotein receptor-related protein). (e.g., col. 6, last ¶; claim 80).

The '146 patent teaches that the expression vectors can be utilized to transform CHO cells (col. 5, ll. 1-8, ll. 15-31; col. 9, ll. 10-17; claims 84-87), particularly DHFR deficient CHO cells (col. 5, l. 15). Further, the expression vectors can contain a CMV or SV40 promoter. (col. 6, ll. 3-6). With respect to the limitation for a "kit" neither claim 90 or the specification particularly define a kit. Therefore, the limitation is interpreted as broadly as reasonable to read on any container. The '146 patent teaches the expression vectors are constructed utilizing

restriction digests and ligation which reactions would necessarily be conducted in a reaction tube, thus meeting the limitation for a kit. (e.g., col. 10, Example 1, bridging to col. 11).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. **Claims 65, 88, 103, 106 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herlitschka et al. (US 6,114,146; see entire document; hereinafter the '146 patent) as applied to claims 59-66, 80-81, 84-87, 89-90 and 115 above, and further in view of Levenson et al. (Hum. Gene Ther. 1998; 9:1233-36; see entire**

document; hereinafter Levenson; reference of record in IDS, filed 04/12/2004) and Keyt et al. (J. Biol. Chem. 1996; 271: 5638-46).

The claims and the teachings of the '146 patent are applied and incorporated herein consonant with what is stated above. (Supra, Rejection No. 2). Additional embodiments are directed to the first selectable gene encoding puromycin resistance or a fluorescence protein.

The '146 patent does not explicitly teach puromycin or a fluorescence protein. However, non-amplifiable selection markers such as puromycin or green fluorescence markers (GFP) were routinely utilized in expression vectors, more particularly dicistronic expression vectors, at the time of invention. Furthermore, it would have entailed nothing more than routine experimentation to mobilize a different selection marker into an expression polynucleotide/vector.

For example, Levenson teaches expression vectors containing GFP, puromycin, as well as hygromycin B, which are utilized in a dicistronic vector that is used to transform mammalian cells and expression a gene of interest encoding a desired protein. (e.g., Abstract; p. 1234, col. 1, ¶ 3).Therefore, it would have been obvious for one skill in the art to modify the vector that the '146 patent teaches with alternative antibiotic resistance gene(s), such as puromycin, or alternatively to incorporate a fluorescence marker. One of skill would have been motivated to make such a modification to expand the range of selectable markers that are used in various cell cultures. Given the nature of the step necessary to mobilize a given gene into a vector backbone, there would have been a reasonable expectation of success to make said modifications to the vector that the '146 patent teaches.In addition, the '146 patent explicitly states that the

expression vectors have applicability in expressing foreign proteins in various cell culture systems. (e.g., col. 10, l. 34).

The reference does not explicitly recite that vascular endothelial growth factor (VEGF)can be expressed.

Expression of proteins of interest, such as VEGF, in cell culture systems was in routine practice at the time of invention. For example, Keyt et al. teach expression vectors encoding VEGF and variants thereof that are used to transform endothelial cells. (e.g., p. 5639, cols.1-2; p. 5640, Figure 1). In any event, the salient point of the instantly claimed vector and the vector that the '146 patent teaches is defined by the structural elements comprised in the vectors. In other words, the inventive step is not what particular foreign protein is being expressed, but primarily the vector, and the corresponding cells that are utilized to express any foreign protein. Furthermore, it would entail nothing more than routine and remedial steps to mobilize any given foreign gene (i.e., selected sequence) into the vector that the '146 patent teaches. Essentially, the vector that the '146 patent teaches is deemed to have the intrinsic characteristic insofar as it can be utilized to express any gene encoding a protein of interest.

As such, it would have been obvious to modify the vector that the '146 patent teaches to express, for example, a vascular endothelial growth factor (claims 81 and 89). One of skill would have been motivated to make such a modification in view of the '146 patent's suggestion that the vector has general applicability in expressing foreign genes in mammalian cells. Moreover, given the level of skill in the art at the time of invention, one of skill could simply mobilize any given gene into the vector that the '146 patent teaches. Thus there would be a

reasonable expectation of success to conduct such a routine step entailing nothing more than cutting and ligating an insert to the vector backbone.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. **Claim 59-90, 93-99, 105-111, 113 and 115-116 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 106-118, 122-152 and 161-164 of copending Application No. 10/019,586, in view of Levenson et al. (Hum. Gene Ther. 1998; 9:1233-36; see entire document; hereinafter Levenson).**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other. In general, the reference claims represent a species of the broader instant genus claims, and both sets of claims are directed to polynucleotides, cells transformed with said polynucleotides and utilizing said compositions to produce desired proteins. The instant and reference claims are respectively directed to polynucleotide versus

vector. However, a vector is deemed a more particular form of a polynucleotide, insofar as it may contain the necessary structural properties to replicate, such as in eukaryotic cells. More particular differences are represented by the reference claims delimiting the selectable marker as GFP (e.g., independent reference claims 106, 112, 138, 139, 151, 161 and 164), while the instant claims are broadly drawn to any selectable gene (e.g., instant claims 59, 72). GFP is not amplifiable (instant claim 62: reference claims 106, 112), so that GFP as a selectable gene is independent of the amplifiable selectable gene. (instant claim 63: reference claim 107). Thus, with respect to vector and GFP, the reference claims represent a species of the at least the broader instant claims directed to polynucleotides and a selectable gene. As such, the reference claims anticipate and necessarily make obvious the instant claims. The instant and reference claims are otherwise indistinguishable as evidence by the comparisons provided hereafter below.

For example, additional embodiments are directed to DHFR as the amplifiable gene. (instant claims: 60, 61, 66: reference claims 107). The fusion polynucleotide is positioned within an intron. (instant claims 67-71: reference claims 110, 113). The fusion gene is positioned within an intron between the promoter and the target sequence. (instant claim 67: reference claim 110). The splicing efficiency is between 80% and 99%. (instant claims 68-69: reference claims 109, 112).

The fusion gene and selected sequence are operably linked to the promoter. (instant claim 70: reference claims 106). An IRES element is present between the target sequence and the fusion gene. (instant claim 71: reference claim 111).

Independent instant claim 72 and reference claim 15 are directed to a polynucleotide and a vector comprising a first and second transcription unit, whereby the instant claim is delimited

to comprising a fusion gene comprising a selectable and an amplifiable gene. Conversely, the reference claim is not delimited to comprising a fusion protein, but dependent reference claim 128 fulfills the limitation for a fusion gene comprising GFP (selectable gene) fused to an amplifiable selectable gene. Another difference between said claims is that reference claim 115 recites that a first and second intron are present, corresponding to the first and second transcription unit. Instant claim 72 does not recite that a first and second intron are present, but dependent claim 73 meets the limitation for a first and second intron sequence, as well as delimiting splicing efficiency of at least 95%, which is also recited in reference claim 115.

The promoters can be same type of promoter (instant claim 74: reference claim 135) or can be CMV or SV40 (instant claims 75, 76: reference claims 136, 137). Further embodiments are directed to at least one promoter being inducible. (instant claims 78: reference claim 137). In addition, the vector can replicate in eukaryotic cells. (instant claim 84: reference claim 142). In sum, but for the slight modifications of polynucleotide versus vector and GFP versus selectable gene, the instant and reference claims are not patentably distinguishable.

Additional embodiments are directed to expressing a heavy and light chain desired product as dicistronic expression products. (instant claims: 82-83: reference claims 140-141).

With respect to limitations directed to antibiotic resistance, the reference claims do no delimit the selectable gene to encode an antibiotic resistance or particularly puromycin resistance. (instant claims 64-65, 97, 106-110). However, puromycin is one of several selectable markers that are routinely utilized in the art of dicistronic vectors and protein expression in mammalian cells, as evidenced by Levenson's teachings. (e.g., Abstract; p. 1234, col. 1, ¶ 3).

Therefore, it would have been obvious to modify the vectors as claimed in the reference claims to include alternative non-amplifiable selectable markers, such as puromycin. One would have been motivated to make such a modification to extend the range of selectable markers that can be incorporated into the expression vectors. Further, given the level of skill at the time of invention, there would have been a reasonable expectation of success in making such a modification, given the remedial nature of the steps necessary to mobilize a given selectable gene into a vector backbone.

Allowable Subject Matter

Claims 102 and 104 are objected to as being dependent from rejected claims, but would be allowable if rewritten in independent form with all intervening claimed limitations. Claim 102 is directed to vector capable of expressing a heavy and light chain of the anti-HER2 receptor antibody, utilizing a two transcription unit dicistronic vector (ultimately vector of claim 72). Claim 104 is directed to expressing the 2C4 anti-HER2 receptor antibody.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DANIEL M. SULLIVAN
PATENT EXAMINER